REMARKS

Reconsideration and withdrawal of the rejections of this application and consideration and entry of this paper are respectfully requested in view of the herein remarks and accompanying information, which place the application in condition for allowance.

I. STATUS OF CLAIMS AND FORMAL MATTERS

Claims 16-62, 64-66 and 68-107 are pending. Claim 16 has been amended; claims 68-107 have been added; claims 63 and 67 have been cancelled.

No new matter is added. Support for the amended claims is found throughout the specification.

It is submitted that these claims are patentably distinct from the references cited by the Examiner, and that these claims are in full compliance with the requirements of 35 U.S.C. §112. The amendments of the claims herein are not made for the purpose of patentability within the meaning of 35 U.S.C. §§ 101, 102, 103 or 112; but rather the amendments are made simply for clarification and to round out the scope of protection to which Applicants are entitled. Furthermore, it is explicitly stated that the herewith amendments should not give rise to any estoppel, as the herewith amendments are not narrowing amendments.

Priority

The application has been amended to indicate that it is a continuation-in-part, rather than a divisional, of the parent application (U.S.S.N. 09/232,469, now U.S. Patent No. 6,451,770). The application has also been amended to reflect the correct filing date of French application Serial No. 96/09402.

The Office Action Summary indicates that certified copies of the foreign priority documents have not been received. A certified copy of French application Serial No. 96/09402, filed on July 19, 1996, was submitted in the parent case, U.S.S.N. 09/232,469, now U.S. Patent No. 6,451,770. Therefore, under M.P.E.P. §201.14(b), additional copies of the foreign priority document are not required.

Double Patenting

Claims 16-67 were rejected under the judicially created doctrine of obvious-type double patenting as allegedly being unpatentable over claims 1-80 of U.S. Patent No. 6,451770. The issue of whether there is indeed double patenting is contingent upon whether the claims are allowed. Upon agreement as to allowable subject matter, if it is believed that there is still a

double patenting issue, a Terminal Disclaimer will be filed at that time. Accordingly, holding the double patenting rejection in abeyance until agreement is reached as to allowable subject matter, is respectfully requested.

II. THE REJECTION UNDER 35 U.S.C. §112, 1ST PARAGRAPH, IS OVERCOME

Claims 16-67 were rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement. The rejections are traversed. The Examiner is kindly asked to consider and make of record the following data and arguments, several of which were submitted in the parent application. The references referred to in this Response were submitted with the parent application; however, copies of the references are enclosed for the Examiner's convenience.

The Office Action states that the specification does not provide guidance for the use of any promoter to drive the expression of BRSV G protein. Böhm *et al.* (1996; cited by the Examiner) recites that strong promoters are useful in DNA immunization to induce CTL response and antibody response. However, in the specific model studied in this document (hepatitis B immunization in mice), plasmids using the CMV promoter induced both types of responses, whereas those using the SV40 promoter only promoted CTL response. Böhm *et al.* concerns intramuscular DNA immunization in mice. On the other hand, Donnelly *et al.* (1997) recites at page 622 that plasmids used for vaccination purposes include a strong enhancer/promoter and that the most frequently used promoters are CMV IE, SV40 early promoter and RSV LTR.

As a result Applicants respectfully do not see how Böhm *et al.*, which concerns intramuscular immunization, is in contradiction with general teaching in the art, and is thus a particular case, could create any prejudice against the use of the known strong promoters like those recited in Donnelly *et al.* for intradermal immunization. Indeed, Böhm *et al.* also confirms that strong promoters are useful in DNA immunization.

Verma *et al.* (1997; cited by the Examiner) also recites that it is preferable to use strong promoters rather than weak promoters (p.240, second paragraph, third and fourth sentences). Note, however, that Verma *et al.* is not prior art, as it was published in September 1997, after the filing date of the PCT application (July 16, 1997) and French application (July 19, 1996) to which this application claims priority.

Therefore, the prior art and the specification provide guidance for the use of known promoters, in particular strong promoters, and not only the CMV promoter.

The Office Action states that the specification does not provide an enabling disclosure for vaccinating against BRSV using an immunogen of BRSV other than the synthetic G gene. It is submitted that the claims are not and need not be limited to the exemplified BRSV. The invention is related to a new manner of vaccinating bovines using DNA vaccines; and, the claims recite "immunogenic compositions" and "methods for inducing an immunological response" such that the claims need not be limited to the exemplified embodiments.

Indeed, the Applicants or Applicants' assignee, in the ordinary course of business, have conducted other experiments that demonstrate that the invention does not apply only to the G gene from BRSV. For instance, below is an assay using the gB gene from the IBR virus. (Applicants or Applicants' assignee will gladly provide the following in Declaration form, but, it is believed that this is not necessary in view of the claim language employed, and the fact that the signature of the undersigned should be sufficient to support the assertions of success below, with the gB gene from the IBR virus, to demonstrate that the invention is broadly applicable.)

Construction of plasmids for DNA vaccination

Plasmids were constructed using the same eukaryotic expression vector pVR1022 (Hartikka *et al.* Human Gene Therapy 1996, 7:1205-1217). This vector contains the immediate early-1 promoter of CMV (hCMVie-1) followed by the 5' untranslated trailer (5'UT) of the hCMVie-1 gene which includes (signals to splice out) an intron. Immediately downstream of this 5' UT is a multiple cloning site followed by the transcription termination region of the bovine growth hormone gene. The IBR gene coding for the gB glycoprotein was cloned in the proper orientation in the multiple cloning site of pVR1012 and the resulting plasmid called pPB148.

DNA for vaccination was prepared from cultures of E. coli K12, DH5alpha F-cells, which harbored the plasmid, according to standard methods. One vaccination dose consisted of 400 micrograms of DNA adjusted to physiological osmolarity.

Experimental design

Twelve specific-pathogen-free calves were obtained by ceasarean section, deprived of colostrum and reared in isolation. The calves were randomly divided in three groups A-C of 4 animals and housed separately. The calves were found free of antibodies against IBR.

The calves were vaccinated three times, at an age of 6 weeks, and 2 and 4 weeks later. Animals in group A were vaccinated with the Pigjet. One vaccination consisted of 5 shots of 0.2

ml in the skin of the shaved upper part of the hind leg. Animals in group B received 2 ml intramuscularly in the neck muscle with a 23 gauge needle. Animals in group C served as a negative control group and the animals were mock-vaccinated with phosphate buffered saline (PBS) intradermally with the Pigjet and intramuscularly in a manner identical to the animals of groups A and B.

Antibody titers are given in Figures A (neutralizing antibody titers measured according to Kaashoek et al. Vaccine 1994, 12, 439-444) and B (serum gB antibody titers measured according to Kramps et al. J. Clin. Microbiol. 1994, 32, 2175-2181) enclosed, showing that the antibody titer is higher in animals of group A.

Van Rooij *et al.* (1998) and Andrew *et al.* (2000) show that vaccination of porcines against two different pathogens (pseudorabies virus and classical swine fever virus) can be performed by intradermal administration of plasmids using the Pigjet.

In view of the foregoing and the claim recitations, there is no reason to consider that the invention could not apply to genes other than G of BRSV; that is, it is clear that the invention is broadly applicable to any bovine DNA vaccine or DNA immunogenic composition.

In conclusion, based on experimentation in the specification on bovine immunization against BRSV by intradermal administration, using a liquid jet apparatus, of a DNA plasmid expressing the BRSV synthetic G gene and extensive knowledge in the art of DNA immunization in veterinary field, the one of ordinary skill in the art will consider:

- that bovine immunization against BRSV by intradermal administration is achievable using a liquid jet apparatus designed to deliver the DNA intradermally,
- that as promoters, in particular strong promoters, other than CMV are usual in the field of recombinant vaccines, including DNA vectors, and are proposed as equivalents to CMV, then teaching of the invention is not limited to the CMV promoter,
- that he will expect that vaccination against other bovine pathogens, e.g. those specifically mentioned in the specification and claims, is also achievable following the invention.

The Examiner is also respectfully requested to note that compliance with 35 U.S.C. 112, first paragraph does not turn on whether an example is disclosed. An Applicant needs not have actually reduced the invention to practice prior to filing. *Gould v. Quigg*, 822 F.2d 1074, 1078, 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987): "The mere fact that something has not previously been

done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it."

Indeed, a specification needs not contain any example of the invention, as the issue is whether the disclosure enables one skilled in the art to practice the invention without undue experimentation. *In re Borkowski*, 422 F.2d 904, 164 USPQ 642 (CCPA 1970).

An Applicant need not describe all actual embodiments of a claimed invention. The first paragraph of Section 112 does not require a specific example of everything within the scope of a broad claim. *In re Anderson*, 176 U.S.P.Q. 331, 333 (C.C.P.A 1973). This is true even in an unpredictable art. *In re Obukowitz*, 27 U.S.P.Q. 2d 1063, 1067 (BOPAI 1993). Such a requirement would have an adverse affect on the patent system. *See In re Angstadt and Griffin*, 190 U.S.P.Q. 214, 218 (C.C.P.A., 1976) (to require a disclosure of every species covered by a claim would force an inventor to carry out a prohibitive number of experiments, and would allow potential infringers to avoid literal infringement by merely finding an analogous embodiment not expressly disclosed)); *In re Goffe*, 191 U.S.P.Q. 429, 431 ("To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for 'preferred' materials in a process . . . . would not serve the constitutional purpose of promoting progress in the useful arts.").

The Section 112, first paragraph, rejection is contrary to the law, as it attempts to limit Applicants to only exemplified embodiments without appreciating that the disclosure in the application, accompanied by the knowledge in the art, is sufficient for the skilled artisan to practice the present invention without undue experimentation

Schrijver *et al.* (1996) confirms the superiority of the present invention over other DNA application methods and mentions the incorporation of a plasmid encoding the F protein of BRSV to achieve protection (see page 134). Therefore, on the basis of the high level of protection obtained against BRSV by the administration of a plasmid containing the synthetic gene that codes for the G protein of BRSV, one of ordinary skill in the art would expect an immunogenic composition and/or a vaccine containing the F protein of BRSV to likewise successfully achieve protection.

Likewise, Ludwig (1983; relevant pages attached), teaches that humoral immunity, especially virus-neutralizing antibodies, are thought to play a major protecting role against BSV-1 (IBR) infections (see p. 186). In addition, Cox *et al.* (1993) teaches the injection of plasmids

encoding the IBR (BHV-1) gD (gIV) gene in cattle (at page 5666). Importantly, the neutralizing antibody titers correlate with the level and duration of viral excretion after challenge, which is the usual criteria for protection evaluation for IBR (see Tables 3 and 4 of reference and Table A, below).

Table A. Relationship between SN titers and the level and duration of viral excretion.

	SN titer before challenge (20 weeks)	Maximum titer and (duration of viral excretion)
150 μg of plasmid	<4	4.8 (<6 days)
500 μg of plasmid	16	3.9 (<6 days)
500 μg of plasmid	32	<1 (< 2 days)
unvaccinated	<4	7.1 (< 8 days)

Cox *et al.* concluded that the "presence of SN antibody suggests that the structural integrity of antigen formed in this manner is retained and also that it can contribute to protective immunity in cattle. (See page 5666, last paragraph).

As discussed above, Applicants observed higher SN titers with intradermal (I.D.) administration using the Pigjet than with intramuscular (I.M.) administration. (See antibody titers in attached Figures A and B, showing that the antibody titer is higher in animals of group A, i.e., animals vaccinated intradermally using the Pigjet apparatus.) Furthermore, Cox *et al.* shows a direct correlation between SN titers and the level and duration of viral excretion, and, together with the teachings of Ludwig, suggest that the increase in the SN titer in the Applicants' experiment correlates with a reduction of the level and duration of viral excretion indicative of protection. Therefore, considering the data of Cox *et al.*, Ludwig, and the Applicants, I.D. immunization according to the instant invention provides a higher level of protective immunity than I.M. immunization.

In addition, the utility of the present invention comes from the use of a needle-less injector to administer plasmids via the I.D. route. This improves protection and also provides advantages in terms of mass vaccination and safety. The data provided illustrates that I.D. administration using a needle-less injector is useful in DNA vaccination against BRSV and IBR. Therefore the instant invention offers an improvement over other DNA application methods. The present invention may also have advantages with respect to meat and hide produced from the bovine.

Accordingly, when the application is considered as a whole, and all of its teachings are appreciated, in light of the case law and the knowledge in the art, especially as shown by the discussion herein, the enclosures herewith and the claim amendments, there is no doubt that the claims meet the requirements of Section 112, first paragraph. Reconsideration and withdrawal of the rejection are requested.

III. THE REJECTION UNDER 35 U.S.C. §112, 2ND PARAGRAPH, IS OVERCOME

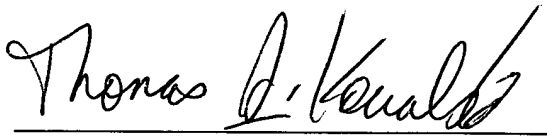
Claim 16 was rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. The typographical error has been corrected, and the claim now recites "said composition", rather than "said composite". Reconsideration and withdrawal of the Section 112, second paragraph, rejection are requested.

CONCLUSION

In view of these amendments and remarks herewith, the application is believed to be in condition for allowance. Early and favorable reconsideration of the application, reconsideration and withdrawal of the rejections, and prompt issuance of a Notice of Allowance are earnestly solicited. The Commissioner is authorized to charge any fee occasioned by this paper, or credit any overpayment of such fees, to Deposit Account No. 50-0320.

Respectfully submitted,

FROMMER LAWRENCE & HAUG LLP

By: 

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION

On page 1, line 2:

This application is a continuation-in-part[divisional] of application U.S. Patent Serial No. 09/232,469, filed January 15, 1999, now U.S. Patent No. 6,451,770[allowed], which in turn is a continuation-in-part of copending International Application PCT/FR97/01322 having an international filing date of 16 July 1997, and designating the U.S. and claiming priority from French application Serial No. 96/09402, filed 19[16] July 1996. All of the above-mentioned applications, as well as documents cited herein and documents referenced or cited in documents cited herein, are hereby incorporated herein by reference. Vectors of vaccines or immunological compositions referred to in[of] documents cited herein or in documents referenced in documents cited herein or portions of such vectors (e.g., part[one or more] or all of regulatory sequences such as DNA for promoter, leader for secretion, terminator), may, to the extent practicable with respect to the preferred host and administration route of this application, also be employed in the practice of this invention.[; and,] DNA for vectors of vaccines or immunological compositions herein can be obtained from available sources and knowledge in the art, e.g., GeneBank, such that from this disclosure, no undue experimentation is required to make or use such vectors[; see]. (See also PCT/IB97/01040, filed July 28, 1997, [and] designating the U.S., and incorporated herein by reference.

IN THE CLAIMS

16. (Amended) A method for inducing an immunological response in a bovine against a bovine pathogen, comprising administering into the epidermis, dermis and/or hypodermis of the bovine an immunogenic composition that comprises a plasmid that contains and expresses *in vivo* in a bovine host skin cell a nucleic acid molecule having a sequence encoding an immunogen of the said bovine pathogen, by a liquid jet intradermal administration apparatus that administers the composition to the bovine: without a needle; and into the epidermis, dermis and/or hypodermis; wherein the administration of said composition[composite] results in the generation of the immunological response in said bovine.